Remarks

The Examiner is thanked for the interview on October 31, 2003, and for the helpful suggestion made at that time regarding amending the terms used in the pending claims to place them into condition for allowance. Accordingly Claims 2, 5, 13, 29 are cancelled, and except for claim 20, the remaining pending claims have been amended as shown. Claim 1 and now-cancelled claim 2 have been combined. The remaining language is supported in the specification, primarily as set out in Applicants' previous response , and certain dependencies have been changed. No new matter has been added.

Regarding the Rejections under 35 USC §112/§101:

The Examiner has maintained the rejection of claims 1-8, 10, 13-19, 23 and 25-29 as indefinite for failing to cite steps involved in the claims method/process. However, in light of Applicants' interview and the present amendments resulting from the Examiner's suggestions, it appears that the rejections are now moot and have been overcome. The previously added term "non-peptide" has been withdrawn and cancelled from all claims. Method claims 15-19 and 23-28 have been amended to reflect a "method of delivery" of the polymersome vesicle and the "at least one encapsulatable molecule" contained therein, which the Examiner has indicated is enabled. "Encapsulatable molecule" is the term used within the specification, and thus is used in the claims, in lieu of the term "active agent" suggested by the Examiner to replace the term "materials." In addition, although Applicants originally used a list of encapsulatable molecules or materials originally provided in claims 14, 23 and 28, Applicants have amended the list as suggested by the Examiner to avoid possible confusion from overlapping terms. Claims defining methods of using the subject polymersomes to remove materials from and environment within a patient have been cancelled.

Accordingly, Applicants respectfully submit that, in light of the present amendments and cancellations, the rejections have been overcome and all claims are in condition for allowance. It is requested that the Examiner reevaluate Applicants' claims and find them to be allowable as amended.

Regarding the Rejections under 35 USC §102(b)/§103:

The Examiner has maintained the rejections under §102(b) and §103. Because the same references (Ding 1998; Cornelissen 1998; Fendler 1984) have been cited in each, Applicants respond to both rejections together.

However, as above, in light of Applicants' interview and the present amendments resulting from the Examiner's suggestions, it appears that the rejections are now moot and have been overcome. Ding *et al.* did not make it obvious to one of ordinary skill in the art that our claimed block copolymer super-amphiphile would assemble into vesicles "without the need of organic solvent" and "without post-assembly stabilization by crosslinking." Accordingly, Ding *et al.* teaches assembly of vesicles from a diblock copolymer that has a block-selective solubility in *two different organic solvents*, rather than a single *aqueous* solvent as required in Applicants' claimed invention. Neither of Ding *et al*'s polymer blocks favors aqueous solution as a hydrophilic polymer does by definition. Since amphiphilic copolymers require at least one block to be hydrophilic, Ding *et al.* does not teach vesicle formation from super-amphiphilic copolymers in accordance with the present invention. See also Applicants' prior arguments of record regarding Ding *et al.* Complete removal of organic solvents after assembly as proposed by Ding is in general very difficult to achieve (in part due to the excellent solubility of the block in that particular solvent), and this particular problem is avoided in Applicants' claimed invention.

Ding *et al.* further teaches preparation of vesicles that requires post-assembly crosslinking for stability in water and therefore the final product is covalently bonded. Applicants' invention does not require post-assembly polymerization or crosslinking (see claim 1). Therefore, crosslinked vesicles (1) have significantly different material properties, for example the non-cross-linked vesicles are fluid whereas the cross-linked vesicles are solid; and (2) have significantly different chemical properties, for example the non-cross-linked vesicles remain an assembly of large number of molecules whereas the cross-linked vesicles can be in principle only one molecule (or the number of molecules that comprises the vesicle is significantly reduced). The Ding *et al.* vesicles can also aggregate due to the "intervesicle linking through the PI chains" (see Properties of the Hairy Hollow Nanospheres, page 6110), which is a problem overcome in

Applicants' invention. Furthermore, Ding *et al.*, alone or combined, fails to teach vesicle formation from super-amphiphiles, and therefore the assembly is not driven by the amphiphilic nature of the copolymer, again an express difference from Applicants' invention. Accordingly, the present invention is neither anticipated by, nor obvious in light of Ding.

Regarding the teachings of Cornellisen *et al.*, the reference teaches self-assembly of peptide-containing molecules based on "chirality" (see first sentence of the publication) and an "attractive interaction between the rodlike headgroups" (last paragraph on page 1428) with "formation of intermolecular hydrogen bonds" (also last paragraph on page 1428). In contrast to Cornelissen *et al.*, Applicants have used *wholly synthetic* (see claim 1), as opposed to peptide based copolymers. Important differences between our claims and the prior art of Cornelissen *et al.* include:

- The absence of amino acids and peptides in a wholly synthetic and not peptide based block copolymer has at least two important implications: It eliminates the possibility of being degraded by proteases either in organisms or in any environment. Thus the wholly synthetic polymers should prove to be more stable.
- Naturally occurring proteases do not distinguish between natural amino acids made by nature and chemically synthesized natural amino acids. Therefore, a clear distinction must be made between copolymers that have been made completely by chemical synthesis but still consist of naturally occurring repeating units and wholly synthetic copolymers that are not based on naturally occurring repeating units.
- A wholly synthetic and non-peptide –based diblock copolymer significantly reduces the immunogenic potential in a patient or animal, for at least three reasons:
    - due to the absence of natural amino acids and peptides which are generally known to be antigenic;
    - due to the fact that the diblock copolymer does not fold into any naturally occurring rigid structure, since the rigidity of the components

or assembly provide stable target for antibody formation or subsequent binding; and

- due to the fact that the diblock copolymer is not chiral, since chirality is also a structural property that is likely to facilitate antibody formation.

Since the assembly of Applicants' claimed polymersomes does not involve intermolecular electrostatic interactions, their formation can be done under a significantly broadened range of conditions (especially physiological conditions), not possible for the Cornelissen compositions. The claimed vesicles form independently of pH (whereas Cornelissen *et al.* specifically teach vesicle formation only at pH = 5.6, at which the electrostatic interactions are optimized; near physiological conditions of pH = 7. No assembly occurs for a related $PIAA_{20}$ copolymer, although no vesicles were specifically disclosed for near the $PIAA_{10}$ polymer). Moreover, the claimed vesicles form independently of the presence of any counter ions.

Consequently, Applicants' invention is neither anticipated by, nor rendered obvious by, Cornelissen *et al.*, who clearly state the importance of peptide-based structure and interactions beyond amphiphilicity for self-assembly. In other words, Cornelissen *et al.* do not teach vesicle formation from super-amphiphiles that depends strictly on the amphiphilic nature of the copolymer, nor would it be obvious from the cited prior art, alone or combined, that super-amphiphiles could form vesicles without further electrostatic or hydrogen-bonding interactions.

Regarding, the teachings of Fendler *et al.*, it would not be known to one of ordinary skill in the art from Fendler that Applicants' claimed block copolymer super-amphiphile would assemble into vesicles "without post-assembly stabilization by crosslinking." As amended, Applicants' claims distinguish from the prior art of Fendler *et al.* for a variety of reasons, including the fact that Fendler *et al.* teaches vesicle stabilization by crosslinking, which is not presently claimed in Applicants' invention. Moreover, Fendler *et al.* does not teach vesicle formation from super-amphiphiles, as required in Applicants' invention, rather the Fendler vesicles are prepared from modified natural lipids. Accordingly, Applicants' invention would be neither anticipated by nor rendered obvious by Fendler *et al.*, since there is no suggestion, alone or combined, that super-amphiphiles could form vesicles in aqueous solutions.

In sum, Applicants respectfully submit that the Examiner's arguments regarding anticipation or obviousness have been overcome in Applicants' present claims for the foregoing reasons in addition to Applicants' reasons of record. Accordingly, it is respectfully submitted

that all pending claims are in condition for allowance, and Applicants' respectfully request that allowance be granted at the earliest date possible.

Finally, the Examiner has rejected claims 7-8 under 35 USC 103(a) over Ding or Fendler for the above stated reasons in further view of Kirpotin (*FEBS Letts.*, 1996). However, for the above-stated reasons, Ding and Fendler fail to teach the presently claimed invention, reflecting the amendments made in response to the Examiner's comments. At the interview, Applicants' representative was concerned because the cited reference as forwarded to Applicants' representative from the PTO was, in part, illegible. In response the Examiner explained that only the abstract was of relevance in the rejection.

In response to the Examiner's rejection, therefore, it is respectfully pointed out that Kirpotin teaches only *liposomes*, as exemplified by vesicles having a cholesterol base. Such compositions are distinctly outside of Applicants' polymersome invention, which by definition at page 17 are assembled from synthetic polymers in aqueous solutions. By marked comparison, "liposomes" are defined in Applicants' specification at page 17, as a "lipid vesicle." Applicants' polymersome is not a "liposome." Unlike the Kirpotin liposomes, which necessarily contain at least 70% lipid as stated at page 117, a polymersome does not include more than 20% lipids or phospholipids. Consequently, polymersomes can be thermally, mechanically, and chemically distinct and, in particular, more durable and resilient than the most stable of lipid vesicles.

In the interview, the Examiner asked for data supporting Applicants' claim to the subject matter of claim 8. Attached hereto is a recently published article by the inventors and several assistants showing the effect of using phospholipid as at least one small amphiphile. See Photos *et al.*, "Polymer vesicles *in vivo*: correlations with PEG molecular weight," *J. Controlled Release* 90:323-334 (2003). The methods previously associated with liposomes, are in the attached article now possible under completely different conditions that previously possible because of the use of Applicants' *completely synthetic* polymersomes.

Accordingly, Applicants' invention would be neither anticipated by nor rendered obvious by Kirpotin *et al.*

In sum, Applicants respectfully submit that all of the Examiner's arguments regarding anticipation or obviousness have been overcome in Applicants' present claims for the foregoing reasons in addition to Applicants' reasons of record. Accordingly, it is respectfully submitted that all pending claims are in condition for allowance, and Applicants' respectfully request that

allowance be granted at the earliest date possible. Should the Examiner have any questions or comments regarding Applicant's amendments or response, the Examiner is asked to contact Applicant's undersigned representative at (215) 575-7034.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0979.

Respectfully submitted,

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